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Maria Rita Mota de Sousa

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Maria Rita Mota de Sousa

Pathophysiology and therapeutic implications of ischemic acute kidney injury

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MARIA RITA MOTA DE SOUSA

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Pathophysiology and therapeutic implications of ischemic acute kidney disease

ORIENTADOR

Doutora Carla Santos Araújo

COORIENTADOR (se aplicável)

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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DEDICATÓRIA

Dedico este trabalho a todos os que me apoiaram ao longo destes fantásticos 6 anos de curso, em especial à Titi, que me ensinou a viver.

Title in English: Pathophysiology and therapeutic implications of ischemic acute kidney disease

Title in Portuguese: Patofisiologia e implicações terapêuticas da lesão renal aguda isquémica

Authors

Maria Sousa – medical student *

Faculdade de Medicina da Universidade do Porto, Portugal

Carla Santos Araújo

Faculdade de Medicina da Universidade do Porto, Portugal

*corresponding author

Adress for reprints

Maria Rita Mota de Sousa

Faculdade de Medicina da Universidade do Porto

Alameda Prof Hernini Monteiro

4200-319 Porto, Portugal

Telephone:00351936275466

e-mail adress: mariaritamsousa@gmail.com

ABSTRACT

Background: Acute kidney injury is a common, complex and serious disorder, especially in hospitalized patients. An increasingly cause of this disorder is ischemia. It is widely recognized that this disease is associated with significantly increased morbidity and mortality, especially in critically ill patients. Despite several advances in the treatment of acute kidney injury, such as pharmacologic treatment and renal replacement therapy, the mortality rate has changed very little over the past twenty years.

Objective: The aim of this review is to summarize the main pathophysiological pathways of ischemic acute kidney injury, as well as what is known about its diagnosis and management, including new therapeutic options.

Methods: Current literature on the definition, epidemiology, diagnosis, biomarkers and management of ischemic acute kidney injury was selected by searching keywords in PubMed, Google Schoolar and ISI Web of Knowledge data bases.

Conclusions: Current data indicate a close interaction between many cell types involved in the pathophysiology of ischemic acute kidney injury. Inflammation seems to be the common factor that connects the different cell types involved in this process. Therefore, therapy targeting specific cell types can reduce the initial and further injury following ischemia, thereby limiting the extent of acute changes and long-term structural and functional alterations to the kidney. Moreover, early treatment of acute kidney injury can be correlated with a better outcome. Since the current biomarkers are not accurate enough to identify initial phases of injury, finding biomarkers such as NGAL, cystatin c and KIM-1, that can stratify correctly the extent of renal damage of each patient as well as the risk of developing chronic kidney disease, could improve outcomes. However, they have high variability and more studies are needed to confirm these properties and to introduce these novel biomarkers in the routine clinical practice.

Key-words: Acute kidney injury; ischemia; biomarkers

RESUMO

Introdução: A lesão renal aguda é uma doença frequente, complexa e séria, especialmente em pacientes hospitalizados. Uma causa cada vez mais frequente é a isquemia. Esta doença está associada a um aumento significativo na mortalidade e morbilidade, particularmente em doentes críticos. Apesar dos diversos avanços no tratamento da lesão renal aguda (terapia farmacológica e terapia de substituição renal), a taxa de mortalidade apenas sofreu uma alteração ligeira nos últimos 20 anos.

Objetivo: O objetivo desta revisão é resumir as principais vias patofisiológicas da lesão renal aguda isquémica, bem como o conhecimento atual relativo ao diagnostico e tratamento, incluindo novas opçoes terapêuticas.

Métodos: Pesquisa nas bases de dados Pubmed, Google Schoolar and ISI Web of Knowledge da literatura atual referente à definição, epidemiologia, diagnostico, biomarcadores e tratamento da lesão renal aguda isquémica.

Conclusões: Estudos atuais indicam uma interação forte entre vários tipos de células envolvidos na patofisiologia da lesão renal aguda isquémica. O fator que coneta os diferentes tipos celulares envolvidos neste processo é a inflamação. Portanto, terapias tendo como alvo células especificas podem dimuir a lesão renal inicial e futura, resultante da isquemia, limitanto a extenção das alterações renais agudas e a longo prazo. Para além disso, o seu tratamento precoce pode ser correlacionado com um melhor prognóstico. Visto que os biomarcadores atuais não são precisos o suficiente para identificar a presença de lesão nas suas fases iniciais, o desenvolvimento de novos biomarcadores como o NGAL, a cistatina C e o KIM-1, capazes de estratifcar correntamente a extensão dos danos renais em cada paciente bem como o risco de desenvolvimento de doença renal crónica, poderá melhorar o prognóstico. Contudo, estas moléculas possuem alta variabilidade, sendo necessários mais estudos para confirmas as suas propriedades e introduzi-los enquanto novos marcadores na prática clínica de rotina.

Palavras-Chave: lesão renal aguda; isquemia; biomarcadores

INTRODUCTION

Acute kidney injury (AKI) is defined as a sudden impairment of kidney function, that leads to the accumulation of nitrogenous and other waste products normally cleared by the kidney[1]. It involves a heterogeneous group of conditions with different ranges in severity, that have in common an increase in the blood urea nitrogen (BUN) concentration and/or an increase in the plasma creatinine concentration, often associated with a reduction in urine output.

Acute kidney injury (AKI) is a common clinical problem with increasing incidence worldwide and high rates of mortality and morbidity, including progression do end-stage chronic kidney disease (CKD)[2]. It accounts for 1% of general hospital admissions and supervenes as a complication in around 7% of all hospitalizations[3]. Despite the significant advances in preventive strategies and critical care, the mortality rate of hospitalized patients with AKI has remained high in the last decades and may exceed 50%[4 5]. Since early recognition and treatment of AKI can be correlated with a better prognosis, it is crucial to develop and invest in novel biomarkers and target therapies[6].

Ischemic AKI represents one of the most frequent types of AKI at the intensive care unit and results from a generalized or localized impairment of oxygen and nutrient delivery to the different kidney cells. The goal of this review is to summarize the main pathophysiological pathways of ischemic AKI, as well as what is known about the diagnosis and management of ischemic AKI, including new therapeutic options.

METHODS

This study has been undertaken as a narrative literature review based on publications related to ischemic acute kidney injury. The goal of the review is to access narrative and systemic literature reviews in order to obtain knowledge regarding the updates in the pathophysiology, diagnostic and treatment practices of acute kidney injury. These studies were identified by searching Pubmed, Google Schoolar and ISI Web of Knowledge data bases, with the terms ACUTE KIDNEY INJURY and/or ISCHEMIA. Only articles written in English were included. Other studies provient from the bibliography of studies included in the initial revision were analyzed and included, if pertinent, in this review.

DEFINITION

Acute kidney injury (AKI) is characterized by an abrupt impairment of kidney function, with a decline in glomerular filtration rate (GFR) that leads to an increase and accumulation of nitrogenous and other waste products, normally cleared by the kidneys[7]. AKI includes a heterogeneous group of conditions with a spectrum that ranges from mild renal impairment to severe renal failure[1 8 9]. However, these have common diagnostic features: an increase in the blood urea nitrogen (BUN) concentration and/or an increase in the plasma or serum creatinine (sCr) concentration often associated with oliguria or anuria[7].

There were two analogous definitions for AKI (RIFLE and AKIN) based on SCr and urine output. However, a single definition for clinical, research and public health proposes is needed, and in 2012 the Kidney Disease: Improving Global Outcomes (KDIGO) proposed a novel definition and classification of AKI[10].

According to these guidelines, AKI is defined as any of the following criteria:

- Increase in SCr by 0.3 mg/dl within 48 hours
- Increase in SCr to 1.5 times from baseline, known or assumed to have occurred within the prior 7 days or
- Urine volume inferior to 0.5 ml/kg/h for 6 hours[1].

The current classification schemes (RIFLE, AKIN and KDIGO), however, have some issues. An example of this fact is that they do not integrate novel kidney biomarkers for early diagnosis, staging and predicting outcomes of AKI. Several studies have shown a subgroup of patients with elevated levels of these biomarkers that did not have the conventional criteria for AKI but have increased risk of RRT initiation and death. However, the variability of the diagnostic performance of many of these novel biomarkers has been a challenge for their translation into routine clinical practice.

EPIDEMIOLOGY

AKI is a widespread problem of epidemic importance. The reported incidences of AKI vary, and are confounded by differences in diagnosis, definition criteria or hospital discharge codification[11 12]. Nevertheless, a quick increase of its incidence is supported by evidence, particularly among patients with acute illness and those undergoing major surgery. A systematic review found that AKI occurred in one in five adults and one in three children hospitalized with acute illness[13].

In western countries, AKI accounts for 1% of general hospital admissions and supervenes as a complication in around 7 % of all hospitalizations[14 15]. This, naturally, has a great impact in health-care costs and resource utilization.[16] Prerenal azotemia accounts for a major part of community-acquired AKI, followed by postrenal and intrinsic etiologies. Prerenal azotemia is the major cause of hospital-acquired AKI, but intrinsic injury is becoming more common.

Despite the advances in prevention and support measures, AKI continues to be associated with high rates of mortality and morbidity, especially in patients in the intensive care unit (ICU). In such patients, mortality rates can exceed 50%. Although mortality rate is decreasing, long-term morbidity is a very important issue. Patients who require dialysis after recovery from severe AKI, have an increased risk for the development of dialysis-requiring end-stage kidney disease[7].

ETIOLOGY

Early recognition and treatment of AKI is crucial to improve the outcome. Once identified, differentiating AKI's subtype will help to address more effective diagnostic and management modalities.

Etiology of AKI involves three major categories: pre-renal, intrinsic and post-renal, but frequently is multi-factorial[17].

- Pre-renal: caused by impaired renal perfusion, with an appropriate renal response (presuming structurally normal kidneys)
- Intrinsic: induced by direct injury to renal parenchyma
- Post-renal: consequence of obstruction to urinary outflow

Table I shows various clinical scenarios sorted into these 3 categories.

PATHOPHYSIOLOGY – ISCHEMIC ACUTE KIDNEY INJURY

One important cause of AKI is ischemia, which can occur for several reasons, such as the use of radiocontrast agents, vasoconstrictive drugs, trauma or sepsis. Isquemic AKI represents one of the most frequent types of AKI at the ICU[18].

Renal ischemia fundamentally affects the structure and function of the renal tubular epithelium. Nevertheless, it also affects the interstitial space and the renal vasculature.

Tubular cell dysfunction and damage

Following a reduction in kidney perfusion, epithelial cells become unable to maintain adequate intracellular ATP for essential processes[19]. This depletion of ATP leads to cell injury and, if severe enough, cell death. All segments of the nephron can be affected but proximal tubular cells are the most commonly injured epithelial cells, because of their high metabolic rate. The outer stripe of the S3 segment of the nephron has also marked microvascular hypoperfusion and congestion after injury because of the unique blood flow, and this can persist and mediate continued ischemia even when cortical blood flow have returned to near normal levels[19]. Endothelial cell injury and dysfunction are responsible for this phenomenon, known as the extension phase of AKI[20]. Other morphological changes include epithelial cell flattening, nuclear loss and loss of brush border of proximal tubular cells [21].

The morphologic changes described previously lead to epithelial cell detachment from the basement membrane, which then tend to accumulate within the tubular lumen forming

granular casts with the potential to block the tubular flow and to reduce GFR in that function unit[19].

Cytoskeletal and structural changes

The integrity of the cytoskeleton is essential for proximal tubular cells, because amplification of the apical membrane by microvilli is crucial for normal cell function[19]. Depletion of ATP leads to quick disruption of apical F-actin by depolymerization mediated in part by cofilin, and redistribution of the cytoskeletal F-actin core. This disruption will cause instability of the surface membrane and formation of membrane-bound extracellular vesicles, which can be either expelled into the tubular lumen or internalized to be recycled[22 23]. The disruption of the actin cytoskeleton also contributes to the loss of adherent and tight junctions. Then there's an increase in paracellular permeability and backleak of the glomerular filtrate into the interstitium[24].

During ischemia, the disruption of the action cytoskeleton also causes loss of cell polarity and function, with decreased reabsorption of sodium and water from the tubular lumen[25]. Due to decreased sodium reabsorption, distal segments of the tubule become activated and send signals to induce afferent arteriolar vasoconstriction (tubulo-glomerular feedback)[26]. Together, all of these mechanisms contribute to a significance reduction in glomerular filtration rate[27].

Apoptosis and necrosis

After an ischemic event, the extent of injury will determine if epithelial cells will be able to recovery or undergo apoptosis or necrosis. Several apoptotic pathways, including the intrinsic (Bcl-2 family, cytochrome c, caspase-9), extrinsic (FAS, FADD, caspase-8) and regulatory (p53 and nuclear factor κB), appear to be activated during ischemic AKI.

Concentrations of proapoptotic (BAX, BAD and BID) and antiapoptotic (Bcl-2 and Bcl-2-like protein 1) members of the Bcl-2 family influence cell survival[19].

Decrease of cellular production of ATP that occurs in ischemia increases cytoplasmic calcium load. This activates proteases, phospholipases and caspases, leading to degradation/destabilization of certain proteins and cell membrane phospholipids[28].

Depletion of ATP also leads to cellular accumulation of hypoxanthine and reactive oxygen species (ROS), further increasing cell damage[28]. These molecules can damage cells by several ways, including peroxidation of lipids in the plasma membrane and intracellular membranes, and destabilization of cytoskeletal proteins and integrins required to maintain cell–cell adhesion. Another property of ROS is their vasoconstrictive effects by scavenging NO[29].

Inflammation

Post-ischemic inflammation contributes to tissue damage and repair in AKI: Ischemia induces endothelial upregulation of cell adhesion molecules such as E-selectin, P-selectin. ICAM-1 and -2, CD99 and proteins of the junctional adhesion molecule family[30]. Additionally, ischemia also promotes downregulation of thrombomodulin. Subsequently, various leukocytes migrate to the activated vascular endothelium. The first cells to accumulate at the site of ischemic injury are neutrophils[31]. Depletion of neutrophils or changes in their function provides only partial protection against tissue injury, suggesting that other leukocytes also mediate injury, such as macrophages, B cells and T cells[32].

Endothelial injury increases endothelin-1's production and decreases endothelium-derived nitric oxide synthase. This enzyme induces vasoconstriction and platelet aggregation, promoting a hypercoagulable state. The combination of leukocyte adhesion and activation, platelet aggregation, and endothelial injury is the basis for vascular congestion of the cortical and medullary microvasculature. Tubular epithelial and vascular endothelial cells

then release inflammatory cytokines, which induce and perpetuate inflammation[2 33]. The main cytokines in this process are IL-6 and IRF-1 [34-36].

There are plenty of immune cells activated in ischemic AKI, including neutrophils, T cells, B cells and macrophages. However, studies that have evaluated the role of these cell populations in ischemic AKI have been conflicting[37]. Macrophages infiltrate the post-ischemic kidney and contribute to renal fibrosis in AKI[38]. Nevertheless, it was also demonstrated that they can differentiate into an anti-inflammatory M2 phenotype, thereby promoting renal tissue repair after ischemia[37]. Li *et al.*[39] shown the essential role of neutrophils and natural killer cells in the innate immune response to renal ischemic injury by mediating neutrophil infiltration and production of interferon gamma.
Some investigations also have demonstrated that T cells can directly contribute to the increased vascular permeability, probably through the production of cytokines such as TNF and interferon gamma[40].

DIAGNOSIS

AKI's clinical evaluation includes a detailed history and physical examination. There's no specific symptom or sign for AKI and the diagnosis of AKI is usually made in the context of another acute illness. Oliguria is the most common sign. However, it is not sensitive or specific[41].

It is important to access risk factors that correlate with the outcome of AKI. These include advance age, male gender, African American ethnicity and diabetes mellitus. However, the most important risk factor is preexisting chronic kidney disease (CKD). Besides increasing the risk for AKI, CKD is a predictor of postoperative AKI and poor surgical outcomes.

Serum creatinine (sCr) concentrations and urea plasmatic concentrations are the most used parameters. If sCr is increased, it is essential to investigate other hypothesis beyond AKI, such as a chronic disease or an acute illness superimposed on a chronic disease. There are

some features that suggest the presence of CKD, such as abnormal sCr concentrations prior to presentation, some risk factors (e.g. hypertension or diabetes) and normocytic anemia. Renal ultrassonography may also be helpful in some settings[42].

CONVENTIONAL BIOMARKERS

sCr and GFR are the main clinical parameters used to diagnose AKI, together with urea, fractional excretion of sodium and proteinuria.

Creatinine is the standard serologic marker used to detect AKI[43]. However, creatinine is a poor biomarker of AKI because its serum concentration is influenced by various extrarenal factors including age, race, sex, body weight and muscle mass. Moreover, substantial rises in SCr are often not seen until one or two days after the initial insult to kidney[10] . Therefore, the diagnosis solely based on sCr is usually delayed and it makes it the treatment and recovery more difficult to achieve. Particularly in the case of ischemic AKI, BUN and sCr are functional biomarkers of glomerular filtration rather than tissue injury biomarkers and, therefore, may be suboptimal for the diagnosis of actual parenchymal kidney damage.

The quest for an ideal biomarker for the diagnosis of AKI is still ongoing. It should have excellent accuracy for the early diagnosis and differential diagnosis of AKI and represent an independent predictor of renal survival and patient mortality[44].

NOVEL BIOMARKERS

Over the past decade, the discovery of new possible biomarkers has gained significant interest. Early treatment of AKI can be associated with a better prognosis and the identification of biomarkers for early diagnosis can improve treatment[6]. Finding patients who are at high risk for developing AKI can stimulate an early approach, and new biomarkers may better stratify the risk and reduce the occurrence of CKD[45].

More than 20 AKI biomarkers have already been studied and are extremely valuable, especially in ischemic injury, both experimentally and in clinical settings in which ischemia is common, as in sepsis and in cardiopulmonary bypass[6]. Among the most studied emerging biomarkers, the most important identified so far are: NGAL, IL-18, KIM-1, cystatin- C, L-FABP, NAG, netrin-1, vanin-1 and MCP-1[43]. NGAL and L-FABP, and KIM-1 and IL-18 (identified later, but with improved specificity).

The most frequently studied are NGAL and Cystatin C. These seem to change earlier than sCr concentration and reflect different aspects of renal injury. For example, Cystatin C concentration is related to changes in GFR[46]; concentration of NGAL is related to tubular stress or injury[47]. Since they change with treatment and recovery, it is suggested that they can also be used to monitor interventions[48]. In addition, they can distinguish a majority of patients who do not have AKI according to creatinine-based criteria, but actually have a degree of kidney stress or injury that is associated with worse prognosis[49].

NGAL

NGAL is a widely expressed 25-kD protein of the lipocalin family [50]. This protein is secreted in vitro by proximal tubule cells as a response to ATP depletion, but in vivo studies have suggested that the thick ascending limb as well as the collecting duct are preferred sites of intrarenal production[51]. Elevated levels of NGAL are detectable in the urine within 3 hours after kidney injury. Plasma NGAL production also increases after AKI because of the increased hepatic production[51].

A recent meta-analysis has demonstrated that serum and urine NGAL levels are not only diagnostic of AKI, but that they also predict the clinical outcomes, such as the need for initiation of dialysis and mortality[49]. Studies in rodents have showed that parental administration of holo – NGAL protects the kidney from ischemia-reperfusion injury, through the decrease of the apoptotic tubular epithelial cells as well as an increase in the amount of

proliferating epithelial cells. Another action of holo-NGAL is the upregulation of the renoprotective enzyme heme oxygenase-1[52]. Together, these studies suggested that NGAL improves the ability of the damaged kidney to recover from injury[53].

Cystatin C

Cystatin C is a cysteine protease inhibitor synthesed in all nucleated cells in the body[43]. It is now considered a superior marker when compared with sCr[54]. Since cystatin C is fully reabsorbed and not secreted under normal circumstances, the urinary excretion of Cystatin C protein correlates with the severity of acute tubular injury. Another advantage compared to sCr is that its concentration is not affected by age, race, gender or muscle mass. Prospective studies showed that the increase of cystatin C precedes in one or two days the increase of sCr.

It is still unclear whether the clinical value of cystatin C is transversal to all forms of AKI. Indeed, in conditions such as obesity, inflammation, thyroid dysfunction and the use of corticosteroids, cystatin C levels may be abnormally e elevated[55].

KIM-1

KIM-1 (kidney injury molecule-1) is a type 1 transmembrane protein that is abundantly expressed in the proximal tubular cells injured by ischemia or nephrotoxins[7]. It is not expressed in appreciable quantities in the absence of tubular injury or in extrarenal tissues. Its functional role may be to stimulate phagocytic properties in tubular cells, enabling them to clear debris from the tubular lumen after kidney injury[56]. Therefore, it has been suggested that KIM-1 may play a role in renal recovery and repair after AKI, which is supported by the late timing of peak changes in urine KIM-1 (2-3 days after injury)[56 57]. However, studies evaluating its prognostic value have reported only modest results[58 59]. Another problem is that the increase of urinary KIM-1, besides suggesting injury, can also translate the repair

response to injury. Therefore, combination with other biomarkers, such as IL-18, could be clinically useful[59].

IL-18

IL-18 is a proinflammatory cytokine that increases after ischemia-induced renal injury[60]. IL-18 appears to have an important role in the inflammatory processes responsible for the exacerbation of renal injury during the extension phase of AKI. Animal models of AKI have demonstrated that the use of therapies that disrupt the IL-18-signaling pathway attenuates renal injury[60]. One option for that is exogenous IL-18 binding protein, which have shown protective renal features[60 61]. Unfortunately IL-18 levels also increase in other conditions, such as inflammatory bowel disease, psoriasis, hepatitis, inflammatory arthritis and systemic lupus erythematosus, which may limit its sensitivity and specificity[43].

To date, several other biomarkers such as microalbumin, *N*-acetyl-ß-D-glucosaminidase, nestin and liver fatty acid-binding protein have been studied for the diagnosis, severity evaluation and, most importantly, the modification of the outcome in AKI[62]. However, more clinical studies are needed to prove the true superiority and cost effectivity of novel biomarkers over sCr.

TREATMENT

Prevention and treatment of AKI is an important clinical issue, as mortality in patients with AKI, despite substantial advances in techniques of resuscitation and renal replacement therapy, remains alarmingly high[63].

Treatment approaches for AKI vary according to the type of insult and, therefore, it is crucial to identify and treat the underlying illnesses[17]. Besides supportive care and treatment of

underlying medical conditions, no specific therapeutic agent has been shown to be effective in the treatment of ischemic AKI[64]. Therefore, risk factors for renal ischemia should be identified and treated promptly, in order to limit further injury and prevent systemic complications[65].

Patients with acute kidney injury usually should be hospitalized unless the condition is mild and clearly resulting from an easily reversible cause[66]. General therapies include optimization of hemodynamic status, correction of fluid and electrolyte imbalances, discontinuation of nephrotoxic medications (e.g. ACE inhibitors, NSAIDs, aminoglycosides) and dose adjustment of administered medications[7]. It is also important to avoid volume overload and hyperkalemia. Large multicenter studies have shown that a positive fluid balance is an important factor associated with increased 60-day mortality[67]. Intake of sodium, phosphate and potassium should be restricted but, occasionally, hypophosphatemia and hypokalemia may occur and supplements may be required[65]. Volume expansion is required when pre-renal azotemia co-exists. In the absence of hemorrhagic shock it is preferable to use isotonic crystalloids rather than colloids as initial management for expansion of intravascular volume[1].

Diuretics are often used to facilitate fluid management and convert oliguric to nonoliguric AKI, since nonoliguric AKI has a better prognosis[68]. However, diuretics can also be harmful since they can reduce the circulating volume excessively, thereby adding a prerenal insult, worsening established AKI. Loop diuretics may decrease oxygen consumption in the loop of Henle by inhibiting sodium transport, thus potentially lessening ischemic injury. Therefore, furosemide might protect against ischemic injury. However, there are only minimal data supporting this theory, and there is some evidence that its use to prevent or treat AKI may be harmful. Indeed, unless in the presence of volume overload, the use of diuretics is not recommended to prevent or treat AKI[69].

The use of dopamine as vasodilator is not recommended. Although administration of low

dose dopamine to healthy individuals causes renal vasodilatation, natriuresis, and increases GFR, several studies showed no effect on renal function, need for dialysis, ICU or hospital length of stay (LOS), or mortality in AKI patients[70]. Similarly, atrial natriuretic peptide and mannitol do not ameliorate AKI[1].

In AKI, hyperglycemia is common due to peripheral insulin resistance[71]. In critically ill patients insulin therapy is recommended, targeting plasma glucose to 110–149 mg/dl (6.1–8.3 mmol/l)[72].

Malnutrition is associated with increased complications and mortality in patients with AKI, so adequate nutrition should be provided. It is recommended a total energy intake of 20-30 kcal/kg/d in patients with any stage of AKI[73]. The amount of proteins suggested is 0.8–1.0 g/kg/d of protein in noncatabolic AKI patients without need for dialysis, 1.0–1.5 g/kg/d in patients with AKI on RRT (2D), and up to a maximum of 1.7 g/kg/d in patients on continuous renal replacement therapy (CRRT) and in hypercatabolic patients. (2D). Enteral nutrition is preferred when possible because it maintains the integrity of the gut, requires less fluid intake, and is less expensive[73]. Furthermore, AKI is a major risk factor for gastrointestinal bleeding[1]. Enteral nutrition should exert protective effects on the risk of stress ulcers or hemorrhage. It has been shown that enteral feeding is associated with improved outcome/survival in ICU patients[74].

Recovery from AKI involves increased expression of several growth factors. Experimental studies have yielded promising results with individual growth factors including insulin-like growth factor-1 (IGF-1), hepatic growth factor, and, more recently, erythropoietin[75]. IGF-1 is a peptide with renal vasodilatory, mitogenic and anabolic properties, which has been demonstrated to accelerate the recovery of renal function in several animal models of AKI. However it wasn't observed in humans[76]. Erythropoietin may have renoprotective effect via its antiapoptotic and antioxidative effects, stimulation of cell proliferation and stem-cell mobilization. However, the usefulness of erythropoietin in human AKI should be further

investigated in the future.

Patients with ischemic AKI are at high risk of recurrent renal damage, volume depletion and hypotension. Therefore, administration of NSAIDs,nephrotoxic drugs and radiocontrast agents, unnecessary anesthesia or surgery should be avoided[65].

Vasopressors

Sepsis and septic shock are major contributing factors to AKI and success has been limited in improving the outcome of this complication[77]. Septic shock is the prototype of a high output–low resistance condition, although severe pancreatitis, anaphylaxis, burns, and liver failure share similar physiologic alterations. Persistent hypotension, despite ongoing aggressive fluid resuscitation or after optimization of intravascular volume in patients with shock, increases the risk of development of AKI[78]. It is not known which vasopressor agent is most effective in this setting.

RRT

RRT is an option for the treatment of AKI with the following goals: to maintain fluid, electrolyte and acid-base homeostasis; to prevent further lesions; to allow renal recovery; to permit other supportive measures, such as nutrition feeding or antibiotics administration, to proceed without limitation or complication.

Whether or not to provide RRT, and when to start, are two of the fundamental questions facing nephrologists in most cases of severe AKI[79]. The optimal timing of dialysis for AKI is not defined. In current practice, the decision to start RRT is based most often on clinical features of volume overload and biochemical parameters of solute and acid-base balance. RRT should be initiated to reduce the systemic complications of prolonged AKI and to allow time for the renal injury to repair[80]. It is widely accepted that patients with severe

hyperkalemia, severe acidosis, pulmonary edema, and uremic complications should be dialyzed emergently[81]. However, if these factors are absent there is generally a tendency to avoid dialysis as long as possible. This decision is based on the well-known risks associated with the therapy, such as hypotension, arrhythmia and complications of vascular access. There is also some concern that RRT may compromise recovery of renal function, and increase the progression of CKD[82]. Nevertheless, many patients requiring RRT will recover enough function not to require long-term RRT[1].

It is crucial to analyze the clinical context, the severity of the disease, the presence of conditions that can be modified with RRT, the presence of comorbilities, and the laboratory tests, rather than single BUN and creatinine values alone. Various options exist for supporting the lost renal function in AKI patients, and selection involves evaluation of the patient's overall condition together with hemodynamic and laboratory status[83]. However it is important to establish reproducible criteria (e.g. biomarker level, fluid overload, severity score) to support the decision to start RRT in AKI patients and to predict its successful discontinuation.

THERAPIES ON INVESTIGATION

1) FENOLDOPAM

Fenoldopam is a pure dopamine type-1 receptor agonist that has similar hemodynamic renal effects as low-dose dopamine but without systemic alpha or beta-adrenergic stimulation. Recent data suggest that fenoldopam may have multiple protective effects, including anti-inflammatory effects independent of any vasodilatory action. However, as an anti-hypertensive drug, it has a significant risk of hypotension[84]. Further large studies are required to determine if it is an effective renoprotective agent.

2) NATRIURETIC PEPTIDES

Atrial natriuretic peptide (ANP) is a 28-amino-acid peptide with diuretic, natriuretic, and vasodilatory activity. Previous animal studies showed that ANP decreases preglomerular vascular resistance and increases postglomerular vascular resistance, thereby increasing GFR. Increases in GFR and diuresis have also been confirmed in clinical studies, preserving renal function in patients undergoing coronary artery bypass surgery or abdominal aortic aneurysm repair[63 77 85]. A recent study in a rat model demonstrated that hANP attenuates renal injury induced by ischemia-reperfusion by attenuation of intrarenal Ang II production, activation of the intrarenal RAS and Ang-II-induced increases in mitochondrial oxygen consumption in kidney tissues[63].

3) RENALASE

Elevated levels of plasma catecholamines accompany ischemic AKI, contributing the inflammatory response[86]. Renalase is a flavin adenine dinucleotide-dependent amine oxidase synthesized by the renal proximal tubules that degrades circulating catecholamines and regulates systemic blood pressure[87]. It also may protect against inflammatory tissue injury by metabolizing catecholamines. A recent study in rats showed that administration of recombinant renalase provides powerful renal protection against ischemic AKI by decreasing necrosis, apoptosis and inflammation of the renal cells[86]. In addition, as plasma renalase decreases after ischemic AKI, it may be useful as a novel biomarker of AKI[88]. These data together suggest that it may have potential for the prevention and treatment of AKI.

4) REMOTE ISCHEMIC PRECONDITIONING

Remote ischemic preconditioning elicited by brief episodes of ischemia and reperfusion in distant tissue may provide protection from subsequent injury[89]. It may attenuate renal injury by inducing the release of several molecules such as damage associated molecular patterns

that are then filtered by the kidney and signal through Toll-like receptors in the proximal tubule epithelia, which may stimulate natural defenses[90]. These defenses can then protect the kidney during subsequent inflammatory or ischemic stress.

Zarbock and colleagues demonstrated that ischemic preconditioning compared with control significantly reduced the rate of AKI and the use of RRT patients undergoing cardiac surgery at high risk of AKI[89]. However, further studies confirming these findings are needed before the general implementation of this procedure.

PROGNOSIS AND PREVENTION

Recovery from AKI is variable and depends on several factors such as etiology and severity and duration of AKI[91]. Prerenal azotemia and postrenal azotemia carry a better prognosis than most cases of intrinsic AKI. The only exceptions are the cardiorenal and hepatorenal syndromes.

AKI is irreversible in approximately 5% to 7% of adults and as many as 16% of elderly patients[17]. Patients with AKI have a higher risk of developing CKD in the future and they are also at higher risk of death[4]. A significant number of patients die from the complications and not because of the disease itself. In the particular case of ischemic AKI, this disease can have distant effects that can induce significant changes in the function of other organs. Several studies have shown the effects of renal ischemia on cardiac tissues, lungs and brain[19].

Besides the high rates of mortality and morbidity, AKI is also associated with significantly longer length of hospital stay and increased cost. It is important for primary care physicians to identify patients who are at high risk of AKI and to implement preventive measures[92].

CONCLUSION

AKI is a problem of epidemic proportions associated with high rates of mortality and morbidity and increased resource utilization. Several factors are implied in these high rates. One of them is the fact that AKI is a disease with heterogeneous presentation and with multiple and related causes, which difficult the early diagnosis.

It is crucial to identify and treat the underlying illness since treatment approaches for AKI vary according to the type of insult. Besides supportive care and treatment of underlying medical conditions, no specific therapeutic agent has been shown to be effective in the treatment of ischemic AKI.

Given the lack of effective therapy and the mortality of this disease, it is needed better understanding of the molecular, cellular and genetic aspects involved in kidney injury in order to develop more target therapies to prevent injury and hasten repair. In the particular case of the pathophysiology of ischemic AKI, it is known that it involves hemodynamic alterations, inflammation and direct injury to the tubular epithelium. Epithelial cell injury lead to functional alterations through direct failure of the cells to transport molecules and ions, or in a indirect way, mediating a decrease in GFR. They can also influence the function of endothelial cells by releasing cytokines and other mediators. Interactions between endothelial cells and leukocytes contribute to continued hypoxia, inflammation, and epithelial cell injury and dysfunction. . Numerous therapeutic targets have been identified that prevent or limit ongoing injury. Inflammation is an important component of this disease and therefore an important target for novel therapies. However, it might be that new strategies to treat or prevent AKI will require the use of compounds that affect multiple pathways or combination therapy that targets several areas, rather than one. Additional approaches to improve repair and minimize fibrosis and vascular dropout will also be critical in limiting the development of CKD, a common complication of AKI.

Effectiveness of therapy may also be enhanced by novel biomarkers. Nowadays, sCr and GFR

are the main parameters used to diagnose AKI. However they have several limitations including low sensitivity and specificity. Novel biomarkers can detect kidney injury earlier than sCr and GFR and therefore improve treatment.

More than 20 AKI biomarkers such as NGAL, KIM-1, cystatin-C and others have already been studied and proved extremely valuable, especially in ischemic injury. However, more clinical studies will be required to prove their true superiority and cost effectivity.

Since AKI is common and harmful all efforts should be focused on minimizing the causes of AKI, establish more uniform diagnosis criteria and develop biomarkers that contribute to an earlier diagnosis as well as developing new therapies more adequate to each etiology.

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Pre renal	**Intrinsic**	**Postrenal**
Hemorrhage Surgical Gastrointestinal Retroperitoneal	Acute tubular necrosis Ischemic Postoperative Prolonged hypotension Sepsis Nephrotoxins Myoglobin Radiocontrast agents Aminoglycosides	Bilateral upper tract obstruction Nephrolithiasis Papillary necrosis Retroperitoneal fibrosis Retroperitoneal lymphadenopathy
Gastrointestinal losses Diarrhea Vomiting Nasogastric suction Enteral fistula	Intratubular obstruction Tumor lysis/uric acid Oxalosis/ethylene glycol ingestion Phosphate nephropathy Light chain nephropathy Acyclovir Indinavir Methotrexate	Obstruction of solitary functioning kidney
Renal losses Diuretics Glucosuria	Acute glomerulonephritis	Lower tract obstruction Prostatic hypertrophy Urethral stricture Bladder mass or stone Obstructed urinary catheter
Skin losses Excessive sweating Burns Erythroderma	Acute interstitial nephritis Proton pump inhibitors Penicillin Fluoroquinolones	Urinary retention Neurogenic bladder Constipation Medications Anticholinergics Antihistamines Alpha1-agonists Beta-blockers Opiates Tricyclic antidepressants
Third-spacing	Atheroembolic disease	

Hypoalbuminemia Pancreatitis Capillary leak		
Renal effective arterial volume Congestive heart failure Cirrhosis	Acute vascular syndrome Aortic dissection Bilateral renal artery thromboembolism Bilateral renal vein thrombosis Thrombotic microangiopathy	
Renal vasoconstriction Hypercalcemia NSAIDs ACEI/ARB Calcineurin inhibitors Vasopressors Iodinated contrast		

Table I: Major causes of acute kidney injury sorted into 3 categories

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ANEXOS

Instructions to Authors

AIMS AND SCOPE

The *Portuguese Journal of Nephrology and Hypertension* is the official organ of the Portuguese Society of Nephrology and is published quarterly. Supplementary issues are also published including selected themes, at the discretion of the Editor-in-Chief, as well as abstracts of the annual congresses of the Society. The Journal is peer-reviewed and is indexed in Thompson Reuter's SciELO Citation Index, with free online access in our websitehttp://www.spnefro.pt/RPNH.

The Journal publishes articles on clinical or laboratory topics of relevance to nephrology, dialysis, transplantation and hypertension. Papers relating to basic immunology, physiology, genetics and epidemiology are accepted when kidney-related. Manuscripts must be submitted in English to the Editor-in-Chief. Only previously unpublished work should be submitted. The Editor-in-Chief has complete editorial freedom.

The Journal complies with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals produced by the ICMJE (International Committee of Medical Journal Editors).

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REVIEW AND PUBLICATION SPEED

All submissions will be subject to an immediate editorial screening process by the Editor-in-Chief after which they will normally be sent to two or three reviewers. The Editor-in-Chief will make every effort to reach a decision on all submitted papers within 8 weeks of receipt. Papers will normally be published in the next issue to go to press after their acceptance. Papers that do not meet the scientific standards of the Journal may be declined by the Editor-in-Chief without further review.

CONTENT TYPES

The Portuguese Journal of Nephrology and Hypertension publishes: 1) Editorials; 2) Review Articles; 3) Original Articles; 4) Case Reports; 5) Letters to the Editor; 6) Nephropathology Quiz; 7) Perspective; 8) Comments.

Editorials

Editorials are usually invited, but authors may propose a paper for the Editor-in-Chief's consideration. They may have up to 2000 words and a maximum of 2 tables or figures. A maximum of 5 references is generally recommended.

Review Articles

Review articles should provide novel insights and comprehensive analyses of topics on Nephrology, and interpretation of the published literature. They are usually commissioned by the Editors. However, unsolicited reviews will be considered. These articles may have up to 5000 words and an abstract of up to 300 words. The use of 3 tables or figures is acceptable. A maximum of 70 references is generally recommended.

Original Articles

An original article must focus on relevant clinical investigation or basic research, and is limited to 4000 words including an abstract with up to 300 words. The order of the text should be as follows: Introduction, Subjects and Methods (any statistical method must be detailed in this section), Results and Discussion. A maximum of 50 references is generally recommended.

Case Reports

Original and succinct description structured in Introduction, Case Report and Discussion. They should not exceed 2500 words (including an abstract up to 300 words) and should not include more than 4 tables or figures. A maximum of 30 references is generally recommended.

Letters to the Editor

Letters must contain information related to an article published in the Journal or may concern a topic of current interest in Nephrology. Letters (maximum of 3 authors) are limited to 500 words and 1 table or figure. A maximum of 5 references is generally recommended.

Nephropathology Quiz

A case report to educate clinicians on the renal pathology. This section includes a concise clinical history, images of histology and discussion. These articles are usually invited and are limited to 2000 words, 8 figures and 20 references.

Perspective

Perspective articles are brief, accessible pieces covering a wide variety of timely topics of relevance to health care and medicine. They are nearly always solicited, although unsolicited articles may occasionally be considered. Perspective articles are limited to 1000 to 1200 words and may include one figure or table. There is a maximum of 5 references.

Comments

Comments usually provide commentary and analysis concerning an article in the issue of the Journal in which they appear. They may also provide commentary concerning an article published elsewhere. They may include 1 figure or table. They are nearly always solicited, although unsolicited comments may occasionally be considered. Comments are usually limited to 1000 words, with up to 10 references.

INSTRUCTIONS FOR AUTHORS

Manuscripts must be submitted online http://rpnh.spnefro.pt. Once you have prepared your manuscript according to the Instructions below, please pay particular attention to the sections on Informed Consent and Ethics and Disclosure.

The text should be double-spaced. The corresponding author should describe the contributions of all authors to the article. Manuscripts should bear the name, address and e-mail of the corresponding author.

Should the manuscript be accepted for publication the authors will be asked to give signed consent for publication in a letter which must contain the statement that "the results presented in this paper have not been published previously, in whole or in part, except in abstract form".

Title Page: The title page should carry the full title of the paper and the first name, middle initial (if applicable) and last name of each author, plus the names and addresses of the respective institutions where the work was done; in the case of different institutions the author(s) should be identified using superscript Arabic numerals. In the case of Portuguese language authors, the title must also be translated into Portuguese.

Abstract: Not more than 300 words. Abbreviations should not be used.
In the case of Portuguese language authors, the abstract must also be translated into Portuguese.

Key-Words: Not more than 6, in alphabetical order, and the terms used (when possible) should be from the Medical Subject Headings list of the Index Medicus. In the case of Portuguese language authors, the key-words must also be translated into Portuguese.

References: Authors are responsible for bibliographic accuracy. All the references, including those with only electronic sources, should be cited according to the "Vancouver Citation Style" which can be consulted on the Internet at: http://library.vcc.ca/downloads/VCC_VancouverStyleGuide.pdf

References must be numbered consecutively in the order in which they are cited in the text. Each reference should give the name and initials of all authors unless they are more than six, when only the first three should be given followed by et al. Authors' names should be followed by the title of the article, journal abbreviations according to the style used in Index Medicus, the year of publication, the volume number and the first and last page numbers. For papers in the course of publication, "in press" replaces the date; the journal name must be given in the references. Manuscripts that are unpublished, in preparation, or submitted, and personal communications should not be cited in the reference list but may appear parenthetically in the text. References to books should contain the author(s) name(s) and initials, the title of the book, followed by place of publication, publisher, year, and relevant pages. Websites must be referenced by the following order: title, URL and access date.

Examples

1. *Journals*:
Hogan J, Mohan P, Appel GB. Diagnostic tests and treatment options in glomerular disease: 2014 update. Am J Kidney Dis 2014;63(4):656-666

2. *Books*:
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